COLLOQUE RECHERCHE
FIRENDO - 7ème ÉDITION -

MODÈLES EXPÉRIMENTAUX : NOUVEAUX HORIZONS POUR LES MALADIES RARES ENDOCRINIENNES

MARDI
5 DÉCEMBRE
2023

FIRENDO
FILIÈRE MALADIES RARES ENDOCRINIENNES

Criblage de molécules repositionnables ou innovantes sur des modèles cellulaires dérivés de cellules souches pluripotentes

I-STEM

Johana Tournois
Responsable plateforme de criblage

I-STEM: Institut des cellules Souches pour le Traitement et l'Étude des maladies Monogéniques

Born in 2005, I-Stem is the result of the combination of two different and independent entities: a Joint Research Unit of Inserm and the University of Evry Val d'Essonne (UMR 861) and the Centre d'Etude des Cellules Souches (CECS) itself supported by the AFM-Telethon.

Collaboration

AFMTÉLÉTHON INNOVER POUR GUERIR

Inserm
Institut national de la santé et de la recherche médicale

université evry val-d'essonne

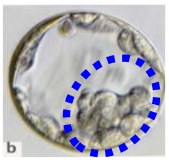
Armed arms of

INSTITUT DES BIOTHÉRAPIES
INNOVER POUR GUERIR

- GÉNÉTHON
  INNOVER POUR GUERIR
  Créé en 1990
- INSTITUT DE MYOLOGIE
  INNOVER POUR GUERIR
  Créé en 1996
- I-Stem
  INNOVER POUR GUERIR
  Créé en 2005

I-STEM Strategies

Human embryonic Stem Cell

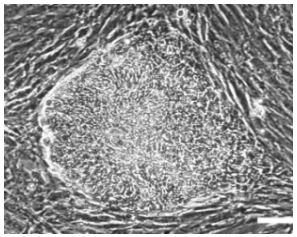


IVF

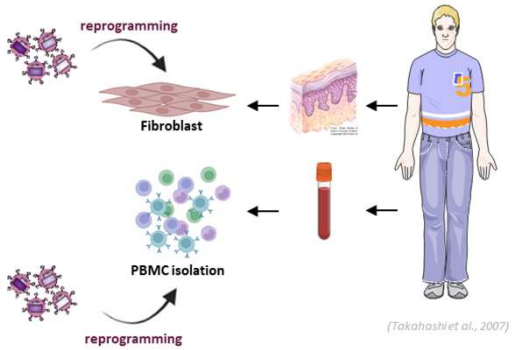
(James A. Thomson et al., 1998)

Nobel prize 2007

PID



Human induced pluripotent Stem Cell

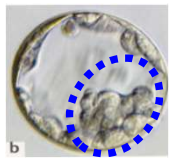


(Takahashi et al., 2007)

Nobel prize 2012

I-STEM Strategies

Human embryonic Stem Cell



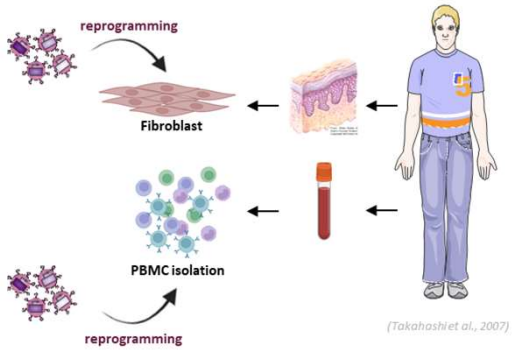
IVF

(James A. Thomson et al., 1998)

Nobel prize 2007

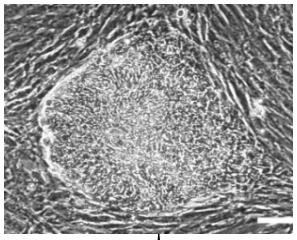
PID

Human induced pluripotent Stem Cell

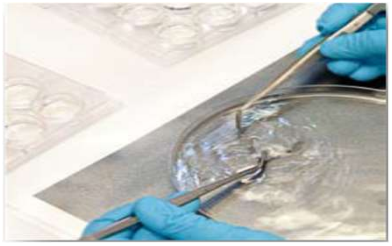


(Takahashi et al., 2007)

Nobel prize 2012



Cellular Therapy



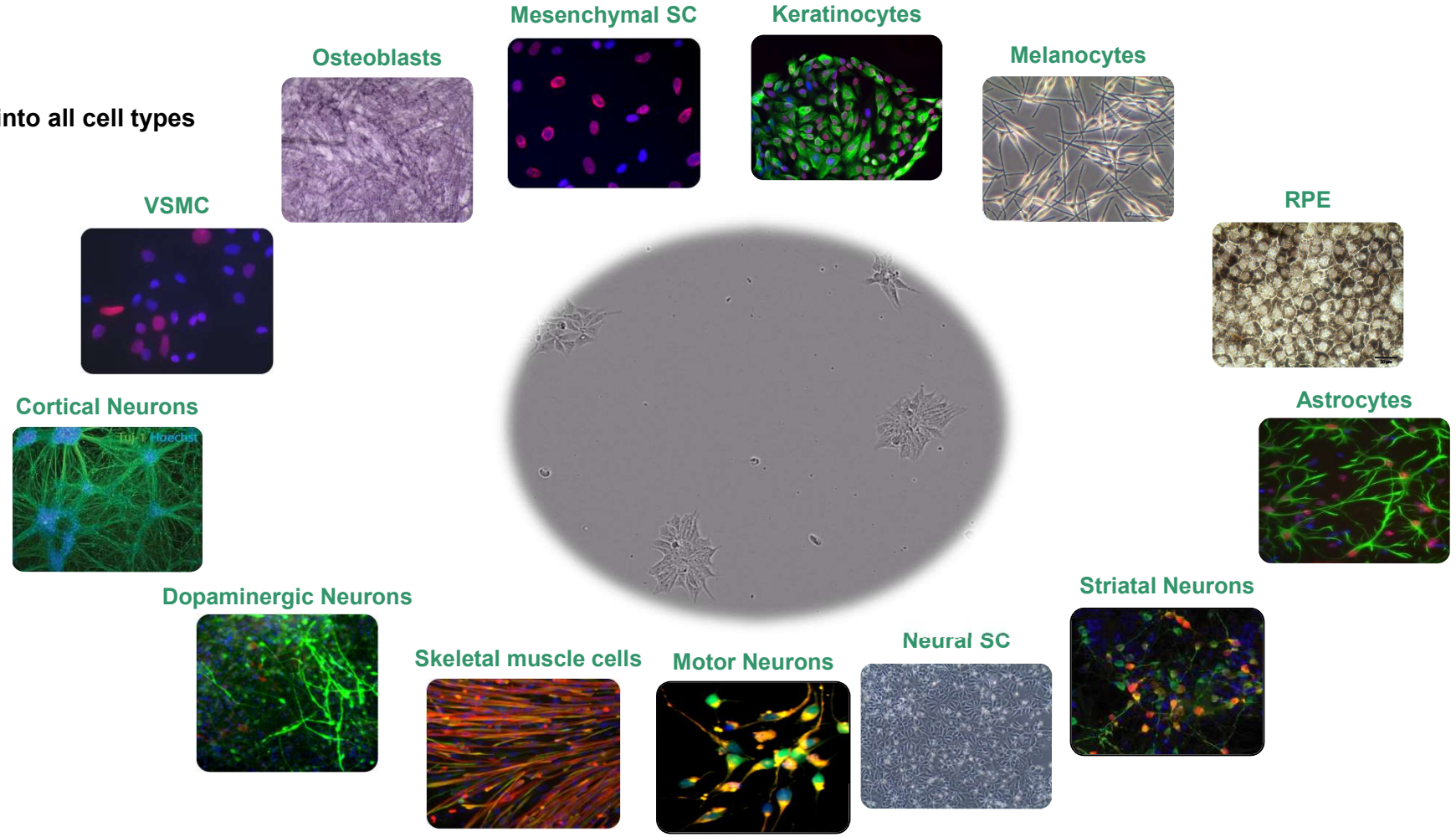
Disease modeling

Drug Therapy

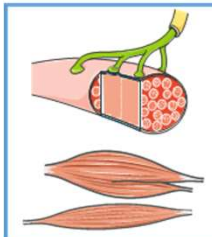
Human pluripotent Stem Cell capacities

First capacity: Self-renewing

Second capacity: Differentiation into all cell types



Diseases investigated at I-Stem

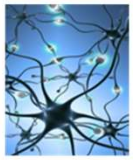


Neuromuscular diseases

Spinal muscular atrophy (SMA)
Steinert myopathy (DM1)
Duchenne myopathy (DMD)

Limb-girdle muscular dystrophy

Sarcoglycanopathies
Dysferlinopathies



Neurodevelopmental diseases

Autistic syndromes
Lesch Nyhan disease

Metabolic diseases

Wolfram syndrome

Genodermatoses

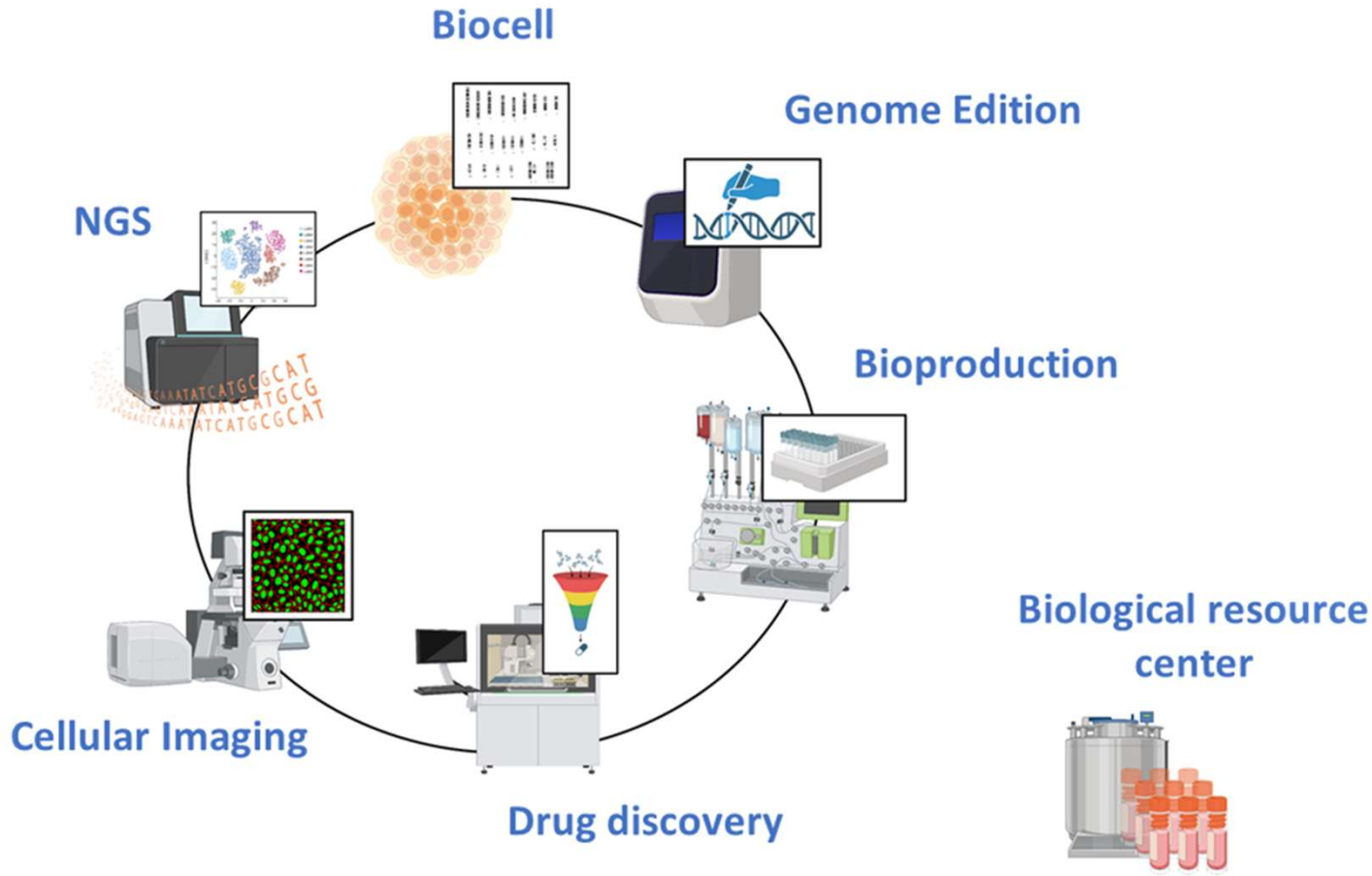
Neurofibromatosis
Epidermolysis bullosa

Retinopathies

Retinitis Pigmentosa
Age-related macular degeneration (AMD)
Alström syndrome

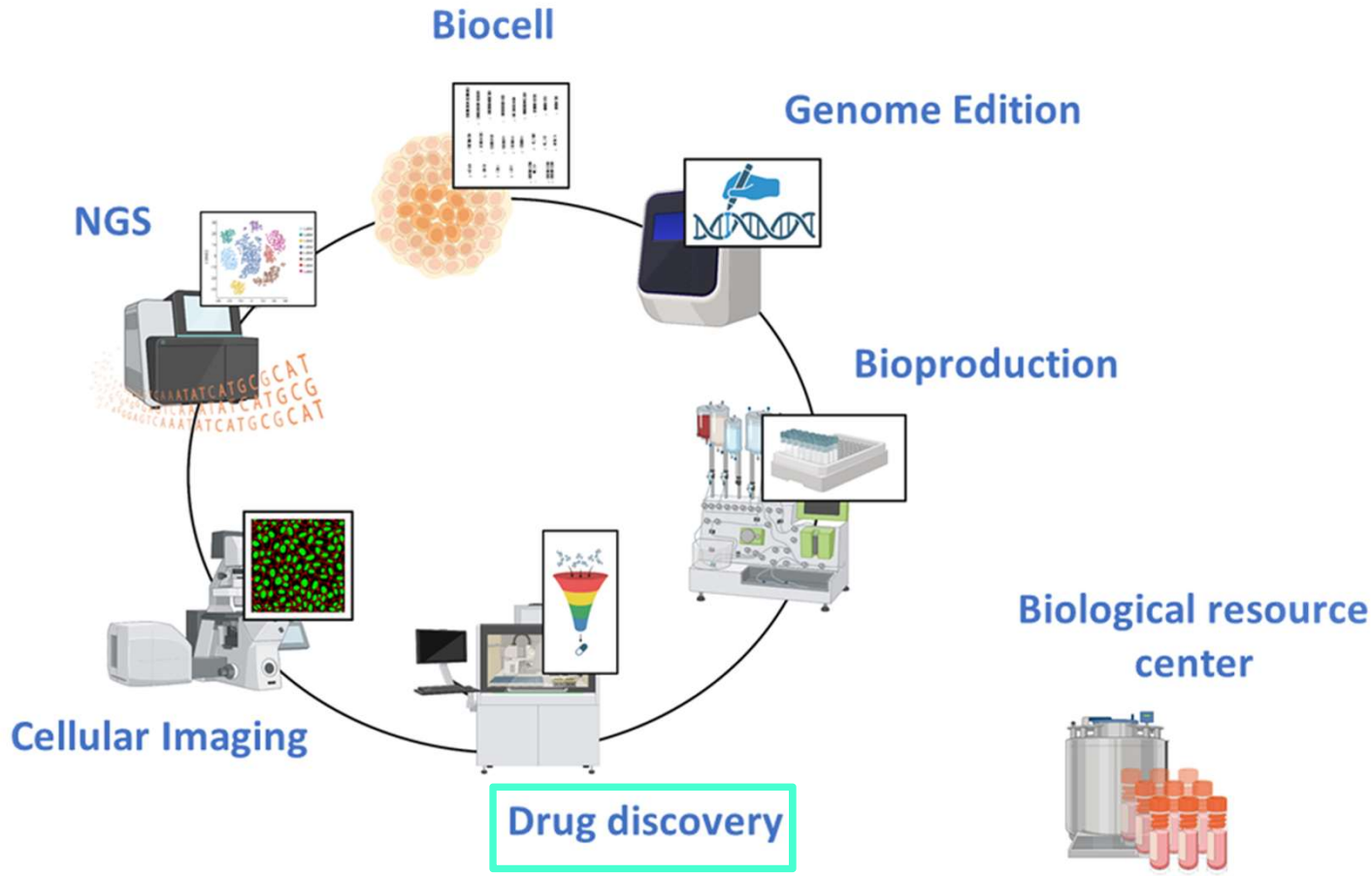
Advanced technologies to support stem cells research

6 domains of expertise

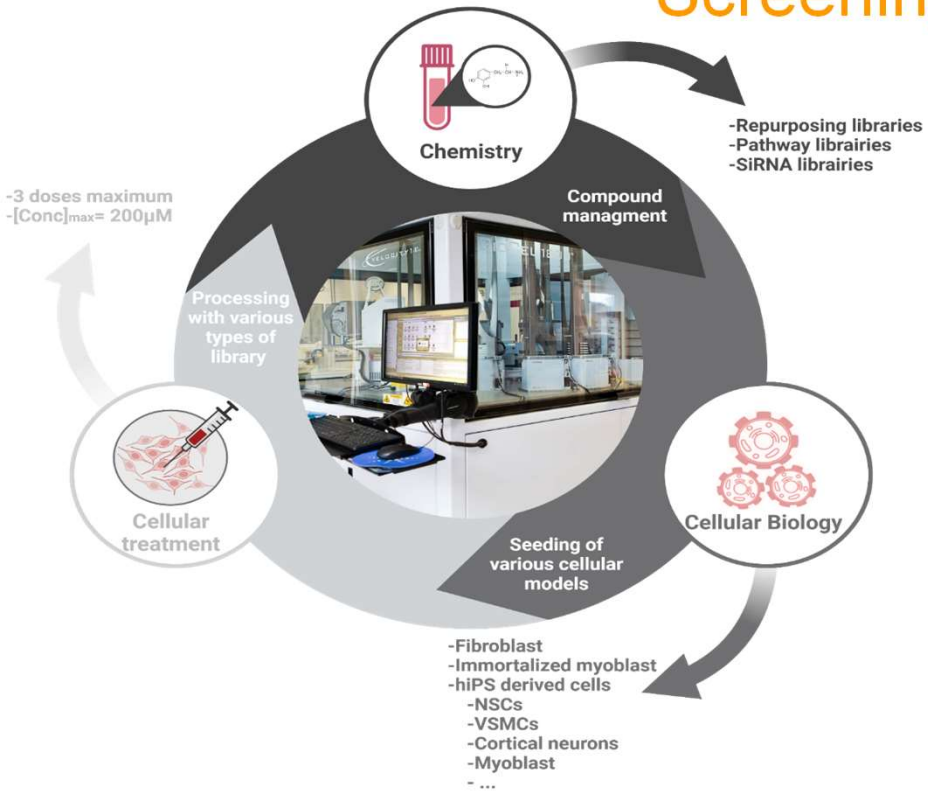


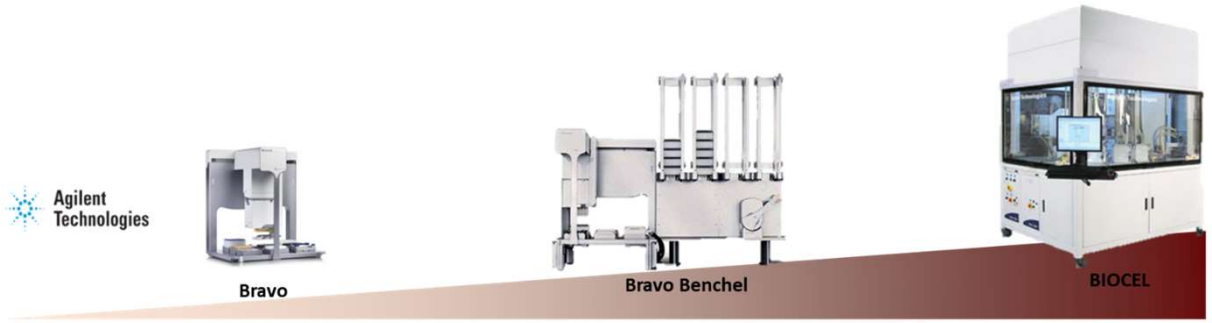
Advanced technologies to support stem cells research

6 domains of expertise

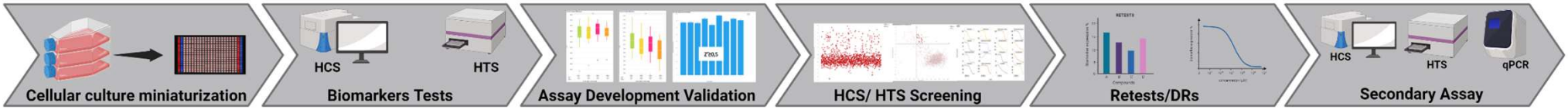


Screening platform organization



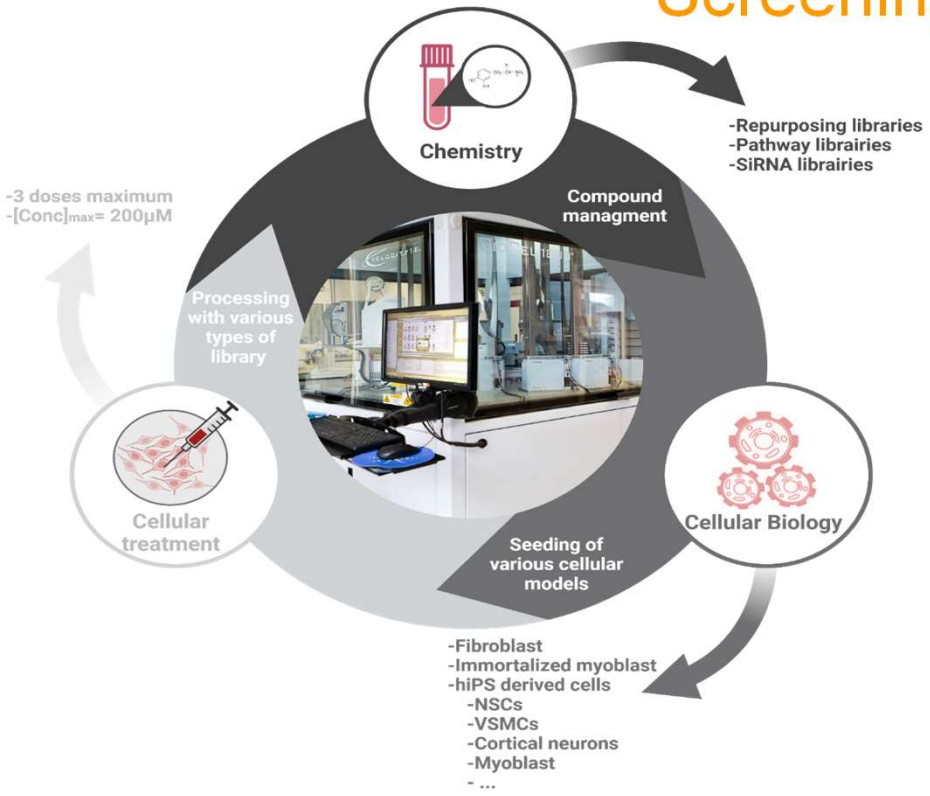


Screening Workflow



Created with BioRender.com

Screening platform organization



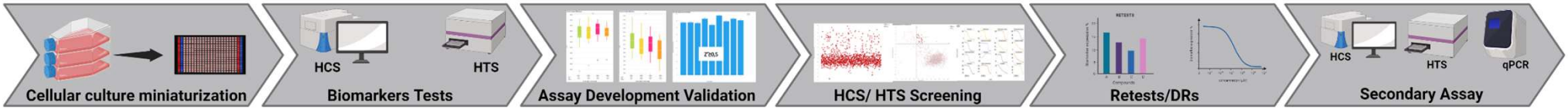
Collaboration or Service provision

- ✓ 38 screening & 10 pathologies
- ✓ >20 Academic / Industrial Collaborations

(Genethon, Institut Myologie,Marseille Medical Genetics Roche, Servier, Pierre Fabre, Pfizer, Ksillink ....)

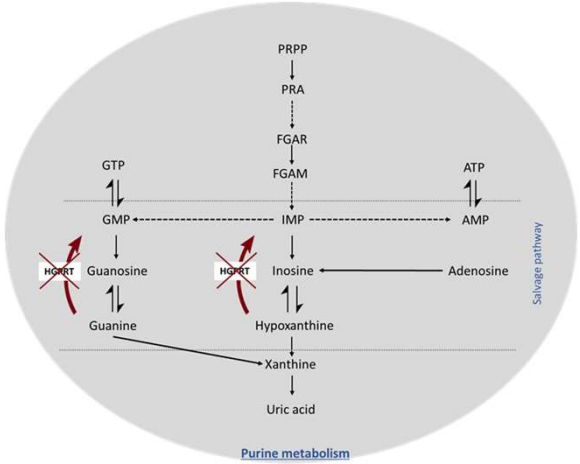
- ✓ 10 publications & 2 Clinical Trials

Screening Workflow



Example of an HTS Screening project

Lesch Nyhan disease Project



- Rare inherited disorder of purine synthesis (incidence 1/250,000)
- Mutations in the HPRT gene located on the X chromosome

SYMPTOMS

Progressive neurodevelopmental disease defined by:

- Motor disorders
- Cognitive-behavioral abnormalities
- Background of hyperuricemia

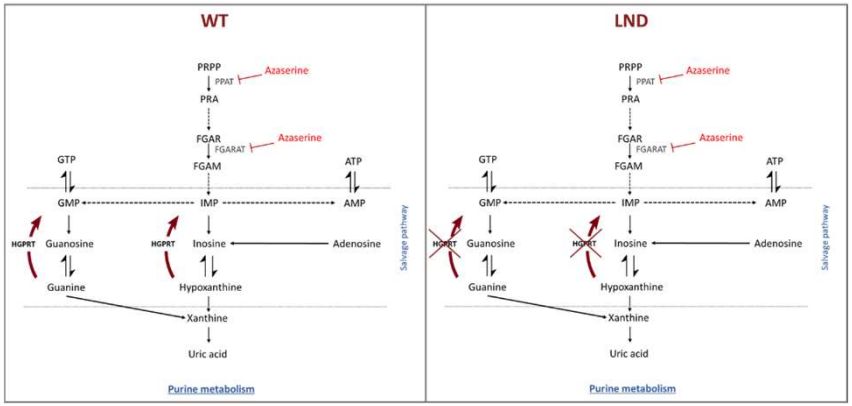
PROJECT OBJECTIVE

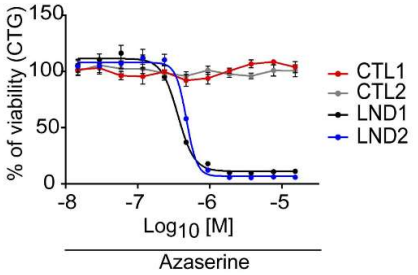
Find compounds that boost purine salvage pathway without activating *de novo* synthesis pathway to prevent the accumulation of uric acid.

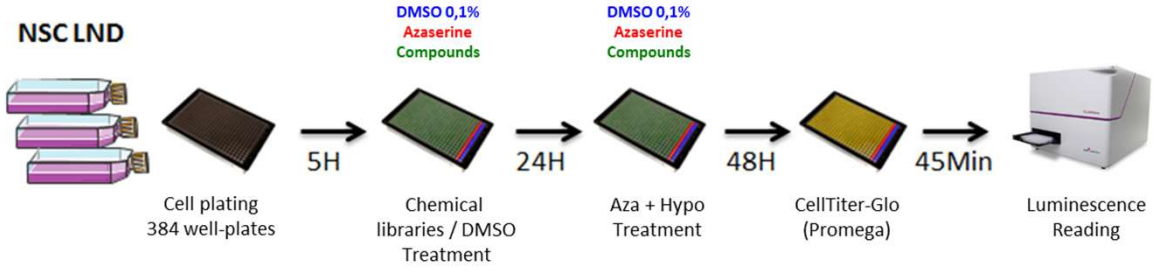
Example of an HTS Screening project

SCREENING STRATEGY

Quantification of viability in neural progenitor cells derived from LND hiPSCs in Azaserine medium that inhibits purine *de novo* synthesis pathway.





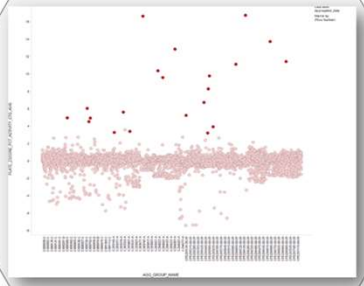


Screening process

Example of an HTS Screening project

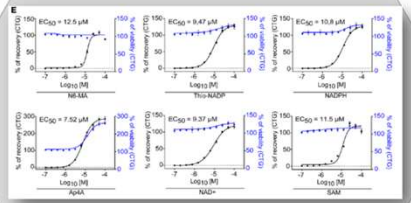
Primary screening

Hit Selection : Zscore > 2 σ



29 hits

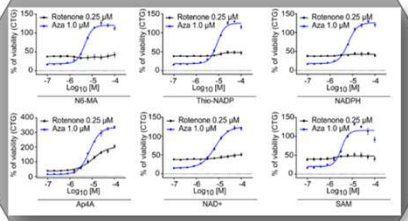
Retests & Dose-Responses



5 hits

Secondary Assays

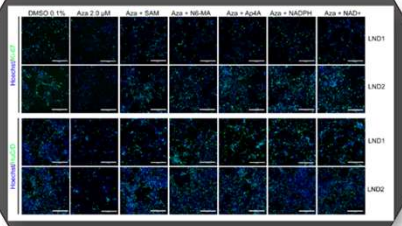
Neuroprotective activity



5 hits

MOA Studies

Compounds restoring LND-relevant neuronal phenotypes



5 hits

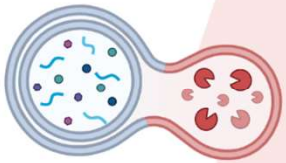
Valorization

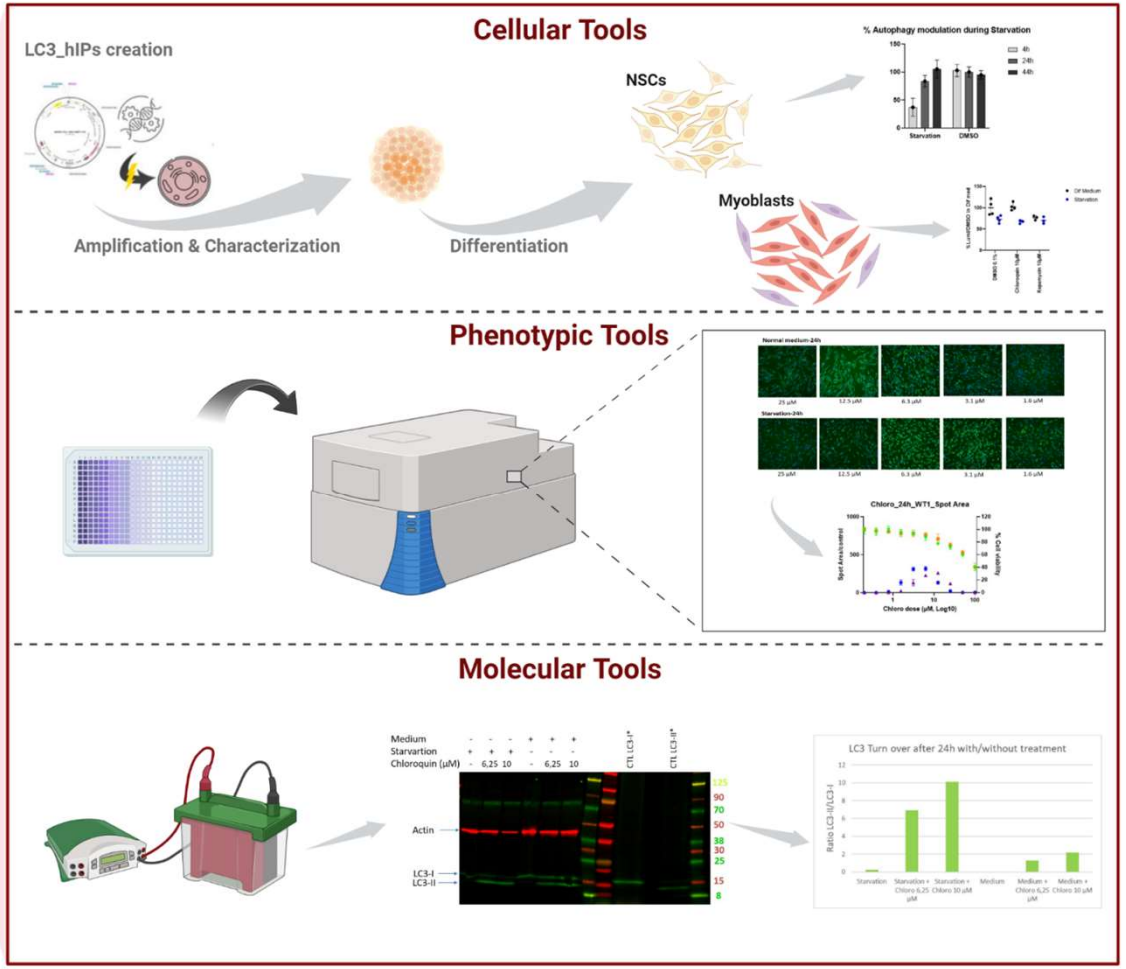
HTS R&D project

DISEASES AFFECTED

-GSD3 (Metabolic disease)
-BPAN (Neurodegenerative disease)
-Dysferlinopathy (LGMD)
-DM1 (Muscular dystrophy)
-DNM2 (Centronuclear myopathy)

AUTOPHAGY





HTS R&D project

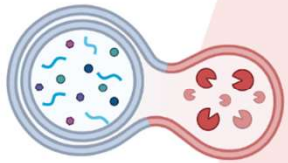
DISEASES AFFECTED

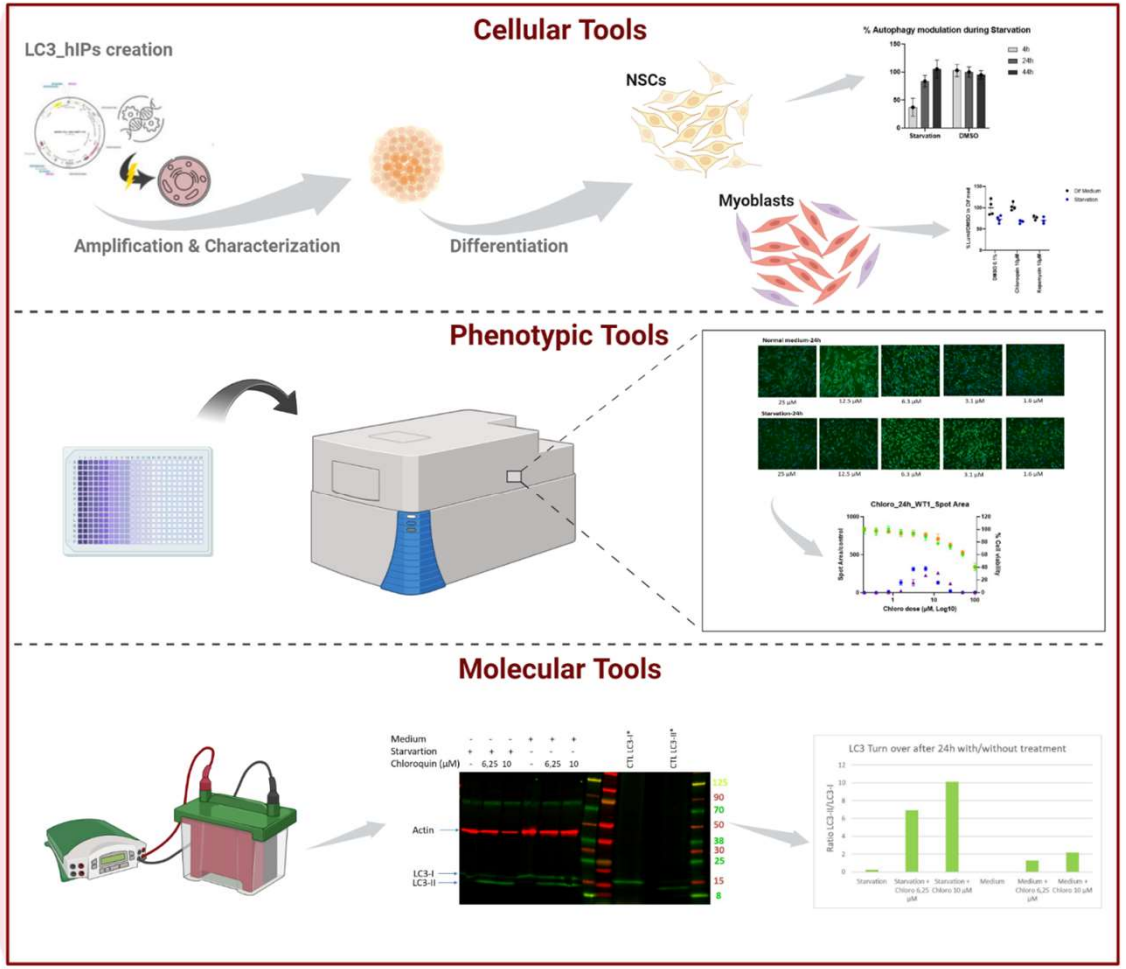
-GSD3 (Metabolic disease)
-BPAN (Neurodegenerative disease)
-Dysferlinopathy (LGMD)
-DM1 (Muscular dystrophy)
-DNM2 (Centronuclear myopathy)

FUTURE DEVELOPMENT TOOLS

-Lysosomal modulation
    -LAMP1/LAMP2
-Iron modulation
    -Ferritin
    -Transferin
    -Biotracker

AUTOPHAGY





The Future of I-STEM's screening platform

PRESENT LIMITATIONS:

- Number of doses tested in parallel
- Range of doses that can be tested

↳ Impossible to consider DRs and combinatorial screening

Obtaining funding SESAME FILLIERE

Région îledeFrance bpifrance

The Future of I-STEM's screening platform

PITCH: Plateforme d'Investigation des Thérapeutiques sur Cellules Humaines

-- >The nanodelivery to identifying medicinal molecules

BECKMAN COULTER

No limitations !

We can consider
-DRs and combinatorial screening
-High-throughput implementation of previously costly biomarker quantification technology

Assembly in progress

Operational in June 2024

Acknowledgments

FIRENDO
FILIÈRE MALADIES RARES ENDOCRINIENNES

Funders

AFM TÉLÉTHON INNOVER POUR GUERIR

Région îledeFrance

bpifrance

université évry val-d'essonne

GENOPOLE

Inserm

Partners

GÉNÉTHON INNOVER POUR GUERIR

INSTITUT DE MYOLOGIE INNOVER POUR GUERIR

Marseille Medical Genetics

Medicinal Chemist:
Jean Marc PARIS

INSTITUT DES BIOTHÉRAPIES INNOVER POUR GUERIR

ksilink

I-Stem
INNOVER POUR GUÉRIR

Suppliers

discngine

Agilent Technologies

Thermo SCIENTIFIC

BECKMAN COULTER

MOLECULAR DEVICES

bio RENDER

BMG LABTECH